REMARKS/ARGUMENTS

STATUS OF THE CLAIMS

Claims 1-19, 21-61, and 201-221 are pending with entry of this amendment, claims 12, 14-17, and 201-221 having been withdrawn and claims 20, 62-200, and 222-303 having been cancelled. Claims 1, 2, 11, 21, 29, 36, and 45 are amended herein. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice to renewal of the claims in their original form and are not to be construed as abandonment or dedication of the previously claimed subject matter or agreement with any objection or rejection of record.

As an initial matter, Applicants would like to thank the Examiner and the Supervisory Patent Examiner for the courtesy extended to the undersigned in conducting an interview with the Examiner and the Supervisory Patent Examiner on October 17, 2006, in which the wording of the independent claims and the art by Barrett et al. and Glickman et al. was discussed with the Examiner. The claims have been amended as discussed in the interview.

Claims 1, 2, 21, 29, 36, and 45 have been amended as discussed with the Examiner to recite that the compositions include the enzyme. Support for the amendments can be found throughout the specification, for example, at paragraphs [0009], [0204], and [0294]-[0296], as well as in claim 11 as originally filed. Claim 2 has been amended as discussed with the Examiner to specify that exhibition of the first and second signals by the first label is independent of any association of the sensor with a solid support. Support for the amendment can be found throughout the specification. For example, the sensors are described throughout the application as exhibiting distinguishable signals from the first label without reference to any solid support. See, for example, paragraphs [0198]-[0199], [0204], [0201]-[0202] and the schematic illustration in Figure 17, [0211]-[0220], [0410], and [0414]-[0419] and the schematic illustrations in Figures 6-11. In certain embodiments, the sensors are present inside cells, where clearly the signals are exhibited while the sensors are not associated with a solid support; see, for example, paragraphs [0221] and [0477] and the schematic illustration in Figure 35. Furthermore, embodiments in which the sensors are associated with a solid support are also described; see, for example, paragraphs [0229]-[0230] and [0420]-[0421] and the schematic illustrations in Figures 12-13.

Applicants submit that no new matter has been added to the application by way of the above claim amendments. Accordingly, entry of the Amendment is respectfully requested.

The Examiner requested in a followup discussion that Applicants point out support in the specification for how the first caging groups are associated with the one or more molecule comprising the substrate. Applicants note that support can be found, for example, at paragraphs [0012], [0150]-[0152], [0209], and [0353]-[0356], which describe, *inter alia*, both covalent and non-covalent association of caging groups. Exemplary embodiments in which caging groups are covalently attached to the substrate are described, for example, in paragraphs [0414]-[0419] and [0427] and schematically illustrated in Figures 6-11 and 17.

Applicants note with appreciation the Examiner's indication of allowable subject matter.

The action of July 12, 2006 included: rejections for alleged indefiniteness (item 2), rejections for alleged anticipation (item 3), rejections for alleged obviousness (items 4-6), response to arguments (items 7-1), and indication of allowable subject matter (item 2). Applicants traverse all rejections and objections, to the extent that they may be applied to the amended claims, for the reasons noted herein.

THE CLAIMS, AS AMENDED, ARE DEFINITE (ACTION ITEM 2)

35 USC §112, Paragraph 2 Rejection of Claims 1-11, 13, and 18-61

Claims 1-11, 13, and 18-61 were rejected for alleged indefiniteness because it was allegedly unclear whether an enzyme is required as part of the composition, and, if not, how the substrate can be converted into a second state from the first state, and whether enzyme activity can be detected without the enzyme. To the extent that the rejections are applied to the amended claims, Applicants traverse.

Applicants maintain that, as detailed in the response to the previous Action, a compound known to be a substrate for a particular enzyme is readily recognized as such, regardless of whether the enzyme is present, and thus the composition need not include the enzyme for the meaning of the claims to be clear. However, in the interest of expediting prosecution, Applicants have amended claims 1, 2, 21, 29, 36, and 45 as discussed with the Examiner to specify that the compositions include the enzyme.

Accordingly, Applicants respectfully request that the rejections be withdrawn.

THE CLAIMS ARE FREE OF BARRETT (ACTION ITEM 3)

Claims 2 and 57-60 were rejected for alleged anticipation under 35 USC 102(b) by Barrett et al. Applicants respectfully traverse these rejections.

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention.

As discussed with the Examiner, Barrett et al. describe immobilization of anti-ligands at predetermined positions on the surface of a solid substrate. According to Barrett et al., caged binding members (for example, caged biotin) are attached to the surface. The caging groups are removed from the caged binding members at predetermined regions on the surface, and anti-ligands are bound to the now uncaged binding members at the predetermined regions. The anti-ligands immobilized on the surface can then be used, for example, to detect ligand binding to the anti-ligands (summarized, e.g., in column 2 lines 38-68). As detailed in Applicants' response to the previous Action, the invention described by Barrett et al. does not correspond with a caged sensor for detecting an activity of an enzyme according to the present invention.

For example, as discussed with the Examiner, Barrett et al. do not teach a caged substrate where the caging groups inhibit the enzyme from acting on the substrate and converting it from one state to another. Barrett et al. thus fail to teach at least a caged sensor including a substrate and first caging groups meeting the limitations of claim 2.

Additional points of distinction are present in the dependent claims, but because independent claim 2 is not anticipated, it is not necessary to address each additional point.

Barrett et al. do not teach a caged sensor including a substrate, a first label, and first caging groups that meets the limitations recited in the claims, as discussed with the Examiner. Accordingly, Applicants respectfully request that the rejections be withdrawn.

THE CLAIMS ARE NOT OBVIOUS (ACTION ITEMS 4-6)

Item 6

Claims 1-11 and 18 were rejected for alleged obviousness under 35 USC 103(a) over Glickman et al. in view of Burbaum et al. To the extent that the rejections are applied to the amended claims, Applicants respectfully traverse these rejections.

Three requirements must be met for a *prima facie* case of obviousness. First, the prior art reference(s) must teach all of the limitations of the claims (M.P.E.P § 2143.03). Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention (M.P.E.P. § 2143.01). Third, a reasonable expectation of success is required (M.P.E.P. § 2143.02). The teaching or suggestion to combine and the expectation of success must be both found in the prior art and not based on Applicants' disclosure (M.P.E.P. §2143).

The combination of Glickman et al. and Burbaum et al. does not meet the requirements for a *prima facie* case of obviousness. First, the combination does not teach all the limitations of the claims.

As discussed with the Examiner, Glickman et al. teach a sandwich assay for measuring tyrosine kinase activity in which tyrosine-phosphorylated substrates are captured on a solid support coated with a first anti-phosphotyrosine antibody. A second anti-phosphotyrosine antibody, which is labeled, is then bound to the phosphorylated substrates captured on the support, capturing the second labeled antibody on the support. Unbound second labeled antibody is removed, and the amount of second labeled antibody bound to the solid support is measured. Glickman et al. thus describe an assay that relies on capture on a solid support.

Claim 1 specifies that the composition includes a cell comprising the caged sensor. As discussed with the Examiner, the assay of Glickman et al. is not performed in a cell. Glickman et al. state that the sample to be assayed may be a purified kinase, a cell fraction, a cell or tissue extract, or a bodily fluid (see column 2 lines 56-59). Further, Glickman et al. state that "Where the biological sample is a preparation of whole cells, prior to assay, the cells to be evaluated are lysed..." (column 5 lines 63-65). As discussed with the

Examiner, the support-bound compositions formed during the assay of Glickman et al. are clearly not inside a cell, and Glickman et al. fail to teach a cell comprising a sensor.

Furthermore, Applicants maintain that Glickman et al. do not teach a first label that exhibits a first signal when the substrate is in its first state and a second, distinguishable signal when the substrate is in its second state, as is specified in claims 1 and 2. The label on the second antibody of Glickman et al. exhibits the same signal regardless of the phosphorylation state of the substrate. The label is merely either bound or not bound to the solid support; it is not responsive to the state of the substrate. However, in the interest of expediting prosecution, Applicants have amended claim 2 as discussed with the Examiner to further clarify this distinction, by specifying that exhibition of the first and second signals by the first label is independent of any association of the sensor with a solid support.

Since Glickman et al. fail to teach at least a cell comprising a sensor, merely adding the caging group from the caged substrate of Burbaum et al. to the substrate and labeled antibody of Glickman does not result in a cell comprising a caged sensor such as that specified in claim 1. Similarly, since Glickman et al. fail to teach at least a sensor including a label that exhibits distinguishable signals depending on the state of the substrate and independent of any association of the sensor with a solid support, adding the caging group from the caged substrate of Burbaum et al. to the composition of Glickman does not result in a caged sensor such as that specified in claim 2.

Additional points of distinction are present in the dependent claims, but because independent claims 1 and 2 are not anticipated, it is not necessary to address each additional point.

The combination of Glickman et al. and Burbaum et al. does not teach all the limitations of the claims. Specifically, at least the following limitations are simply not taught by the combination: a cell comprising a caged sensor, and a first label whose signal is responsive to the state of the substrate and independent of any association of the sensor with a solid support. Furthermore, motivation to combine the teachings of the references is lacking. No suggestion to combine the teachings is found in the references. In addition, there is no reasonable expectation of success, since the suggested combination does not result

in the present invention. Applicants respectfully request that the rejections be reconsidered and withdrawn.

Item 7

Claims 13, 19, and 61 were rejected for alleged obviousness under 35 USC 103(a) over Glickman et al. in view of Burbaum et al. further in view of Kris et al. To the extent that the rejections are applied to the amended claims, Applicants respectfully traverse these rejections.

The combination of Glickman et al., Burbaum et al., and Kris et al. does not meet the requirements for a *prima facie* case of obviousness. For example, the combination does not teach all the limitations of the claims.

As described above, the combination of Glickman et al. and Burbaum et al. fails to teach all the limitations of claims 1 and 2, from which the claims at issue depend. For example, the combination of Glickman and Burbaum fails to teach at least a cell comprising a caged sensor or a first label whose signal is responsive to the state of the substrate and independent of any association of the sensor with a solid support. Merely adding instructions for use in a kit or the identity of the enzyme as a protease from Kris et al. does not result in the claimed invention; the combination still fails to teach at least a first label whose signal is responsive to the state of the substrate and independent of any association of the sensor with a solid support or a cell comprising a caged sensor. Moreover, motivation to combine the teachings of the references is lacking. No suggestion to combine the teachings is found in the references. In addition, there is no reasonable expectation of success, since the suggested combination does not result in the present invention. Accordingly, Applicants respectfully request that the rejections be withdrawn.

Item 8

Claims 47-49 and 52-54 were rejected for alleged obviousness under 35 USC 103(a) over Glickman et al. in view of Burbaum et al. further in view of Fischer et al. To the extent that the rejections are applied to the amended claims, Applicants respectfully traverse these rejections.

The combination of Glickman et al., Burbaum et al., and Fischer et al. does not meet the requirements for a *prima facie* case of obviousness. For example, the combination does not teach all the limitations of the claims.

As described above, the combination of Glickman et al. and Burbaum et al. fails to teach all the limitations of claims 1 and 2, from which the claims at issue depend. For example, the combination of Glickman and Burbaum fails to teach at least at least a cell comprising a caged sensor or a first label whose signal is responsive to the state of the substrate and independent of any association of the sensor with a solid support. Merely adding a cellular or subcellular delivery module from Fischer et al. does not result in the claimed invention; the combination still fails to teach at least a first label whose signal is responsive to the state of the substrate and independent of any association of the sensor with a solid support or a cell comprising a caged sensor.

In addition, motivation to combine the teachings of the references is lacking. No suggestion to combine the teachings is found in the references. Furthermore, there is no reasonable expectation of success, since the suggested combination does not result in the present invention. Accordingly, Applicants respectfully request that the rejections be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, an interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 337-7871 to schedule an interview.

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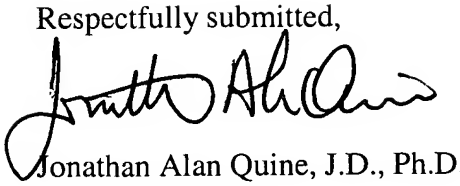
Respectfully submitted,



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Attachments:

1) A petition to extend the period of response for <u>one</u> month;
2) A transmittal sheet;
3) A fee transmittal sheet;
4) Information Disclosure Statement, Statement under 37 C.F.R. §1.97(d)-(e)(2), Form-1449, 3 references; and,
5) A receipt indication postcard.

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